UNITED STATES PATENT AND TRADEMARK OFFICE

	Examiner: ARNOLD, Ernst V.	Art Unit: 1616
Re:	Application of:	KIM, In-San, *et al.*
	Serial No.:	10/528,749
	Filed:	March 22, 2005
	For	**BONE-FILLING COMPOSITION FOR STIMULATING BONE-FORMING AND BONE-CONSOLIDATION COMPRISING CALCIUM SULFATE AND VISCOUS BIOPOLYMERS**
	Confirmation No.:	8173

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

I, Byung Chae Cho, declare and state:

1. My educational background includes a M.D. Degree in Plastic Surgery Department from Kyungpook National University and a Ph. D in Craniofacial Plastic Surgery from Kyungpook National University. I completed my medical residency in 1992 at Kyungpook National University Hospital in the field of plastic and reconstructive surgery. My postdoctoral work was in the field of Craniofacial Plastic Surgery at Kyungpook National University. I also completed a fellowship in 1996 at Kyungpook National University Hospital in the field of Plastic and Reconstructive surgery.

2. I presently hold the position of Professor, Department of Plastic and Reconstructive Surgery, College of Medicine, Kyungpook National University.

3. My expert opinion and conclusions, as set forth in this Declaration, are based upon my familiarity with the invention taught by the above-identified patent application, for which I am a co-inventor, together with my expertise and experience in the field of plastic and reconstructive surgery as evidenced by my 165 publications and 13 years of research and teaching in academic and clinical arts relating to plastic and reconstructive surgery.

4. My further professional experience and publications are summarized by my Curriculum Vitae, which is attached as Exhibit A.

5. I have read and understood the Examiner's February 7, 2007 Office Action, which rejects all of the pending claims. In particular, I understood that the Examiner has taken the position that the invention described in claims 1-5 and 7-8 would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the combination of US Patent Publication 2002/0071827 (hereinafter "Petersen et al.") in view of U.S. Patent No. 5,281,265 (hereafter "Liu"). I have also read these references and understand their respective disclosures.

6. I believe that I am well-qualified as an expert in the field to analyze these references. I further believe that I am well-qualified as an expert in the field to render an opinion concerning what one of ordinary skill in the art would be taught by the references cited against this patent application.

7. In my opinion, the bone-filling compositions claimed by applicants herein would not have been obvious in view of the information contained in the combination of the references relied upon by the Examiner. My opinion is based upon my extensive experience as a researcher and clinician in the field of bone transplantation and bone-extension. The reasons for my opinion are set forth in the following paragraphs

8. First, the Declaration provides reasons why the subject matter claimed in this patent application is not rendered obvious to the combination of references relied upon by the

Examiner to reject the examined claims. Secondly, the Declaration sets forth comparative data which shows the bone-filling compositions claimed herein have an unexpectedly superior ability to stimulate bone-formation and bone-consolidation.

9. My review of Petersen et al. leads me to the conclusion that it only describes bone graft substitute compositions containing calcium sulfate, a mixing solution such as water and a plasticizing substance such as carboxymethylcellulose. Peterson et al. teaches the composition containing 80-120 parts by weight calcium sulfate and 1-40 parts by weight plasticizing agents such as carboxymethylcellulose.

I understand that the Examiner alleges that "Petersen et al. teach that the composition can contain 0.1-2 weight % sodium bicarbonate as well as other inorganic elements and inorganic elements and inorganic salts thus establishing a guideline for the addition of carbonate salts (Page 2, [0019], page 4 [0051]" based on my review of the Examiner's comments on page 4, first paragraph of the Office Action concerning the $CaCO_3$, $MgCO_3$ and $CaCO_3$·$MgCO_3$ of the claimed composition.

I have thoroughly read Petersen et al. and find no mention of including the $CaCO_3$, $MgCO_3$ and $CaCO_3$·$MgCO_3$ in the claimed invention. Contrary to the Examiner's position, the reference teaches that the compositions can include, at best, 0.1-2% sodium bicarbonate by weight and does not teach or guide including $CaCO_3$, $MgCO_3$ and $CaCO_3$·$MgCO_3$. I have copied the passage referred to by the Examiner below:

> [0019]...The composition may include a bioactive agent selected from the group consisting of demineralized bone matrix, growth factors, hyaluronic acid, bone morphogenic proteins, bone autograft, and bone marrow, etc. The composition may include sodium bicarbonate. For example, the composition may include 0.1-2% sodium bicarbonate by weight for creating a porous structure in the resultant composition. Possible embodiments of the bone graft substitute composition of the present invention may include at least one additive selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, inorganic element, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer cell scaffolding agent with parenchymal cells, angiogenic drug, demineralized bone powder, collagen lattice, antigenic agent, cytoskeletal agent, mesenchymal stem cells, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone, cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxyapatite, penetration enhancer, bone allograft, and chunks, shards, and/or pellets of calcium sulfate.

[0050] The resulting bone graft substitute can also be used as a carrier, for example, by mixing it with other materials such as allografts, antibiotics, and growth factors. This can the composition with versatility and flexibility by allowing a user to formulate a mixed composition according to a desired application. *Emphasis added.*

I therefore assert that contrary to the Examiner's position, paragraphs [0019] and [0050] of Petersen et al. do not teach or suggest adding calcium carbonate, magnesium carbonate and their complex form. As an expert in this field, it is my opinion that one cannot infer that the claimed three salts required by the claims can be derived from Petersen et al. The Examiner's position is unfounded hindsight.

10. I have also studied Liu which was cited by the Examiner as providing some of the information which when considered with Petersen et al. completes the obviousness rejection and supposedly cures the deficiencies of Petersen et al. teachings as they pertain to the claimed invention. The Examiner has taken the position that Liu cures the deficiencies of Petersen to produce the claimed composition. I respectfully disagree.

Liu describes surgical cements including a cementing component such as calcium sulfate, a setting component, and water. The reference also teaches that the surgical cements can further include a biocompatible filler.

At paragraph bridging pages 4 and 5 of the Office Action, the Examiner states as follows:

Liu teaches the resorbable calcium sulfate surgical cements for use in medical applications such as orthopedic and maxillofacial surgeries and dental applications comprising a **biocompatible filler selected from the group consisting of calcium carbonate, magnesium carbonate and mixtures thereof** (Claims 1, 15 and 16). Liu teaches the weight ratio of the fillers to the cementing components can be up to 4 to 1 (Column 4, lines 41-53). Liu states that biocompatible filler component is substantially inert thus establishing that $CaCO_3$, $MgCO_3$ and $CaCO_3$:$MgCO_3$ are secondary inert ingredients in the cement composition; thus they are **optional and not required** for the cement to function (Column 4, lines 41-57; Column 5, line 35 and claims 15 and 16).
Emphasis added.

As an expert in this field, I believe that, contrary to the Examiner's position, Liu would not provide one of ordinary skill with the required teachings or suggestion to address the

shortcomings of Petersen et al. by including $CaCO_3$, $MgCO_3$ and $CaCO_3 \cdot MgCO_3$. I have copied passages referred to by the Examiner for the biocompatible filler below:

> 1. A surgical cement for use in medical applications such as orthopedic and maxillofacial surgeries and dental applications comprising a hardened cement formed from a mixture comprising a cementing component selected from the group consisting of calcium sulfate-containing components, calcium succinate, calcium malate, calcium malonate, calcium maleate, hydrates thereof and mixtures thereof, said cementing component having a solubility in water at 25°C in the range of about 0.5×10^{-2} M to about 20×10^{-2} M; a setting component selected from the group consisting of water soluble, neutral salts of polyfunctional carboxylic acids containing 2 to about 10 carbon atoms, water soluble dibasic phosphate salts and mixtures thereof; and water in an amount effective to form a paste from said mixture which paste hardens into said hardened cement which is biocompatible, provided that the weight ratio of said cementing component to said setting component in said mixture is in the range of about 1:1 to about 5:1.
>
> 15. The surgical cement of claim 1 wherein said mixture further comprises a biocompatible filler component which is substantially inert with respect to the interaction between said cementing component and said setting component during said hardening.
>
> 16. The surgical cement of claim 15 wherein said biocompatible filler component is selected from the group consisting of tetracalcium phosphate, tricalcium phosphate, calcium alkali phosphate ceramic, bioglass, calcium carbonate, calcium hydroxide, calcium oxide, calcium fluoride, magnesium hydroxide, hydroxyapatite, calcium phosphorus apatite, magnesium oxide, magnesium carbonate, magnesium fluoride, collagen, other resorbable biocompatible materials and mixtures thereof.

The surgical cements of the present invention can incorporate biocompatible fillers. Such fillers can be bioresorbable or non-resorbable. The fillers included are preferably substantially inert with respect to the interaction between the cementing component and the setting component during hardening. Such fillers include, for example, calcium oxide, magnesium oxide, calcium fluoride, calcium carbonate, collagen, alpha-tricalcium phosphate, beta-tricalcium phosphate, hydroxyapatite, calcium phosphate apatite, bioglass and other calcium phosphate-containing ceramics and the like and mixtures thereof. The weight ratio of the fillers to the cementing components can be up to about 4 to 1. These fillers can be in the form of particles, such as either granules or powder, which preferably have particle sizes in the range of about 3 microns to about 200 microns or about 400 microns.
See page 4, column 4, lines 41-57 of the reference.

For convenient application, the cement of the present invention can be prepared as

a paste first. The paste can be introduced into the bone defects or implantation site before it becomes hardened. Alternately, the cement can be premolded to any shape before use. For example, in the drug release system, the required amount of drug may be mixed with the cementing component, the setting component, and optionally the filler, and water to form a paste.
See page 5, column 5, lines 28-36. *Emphasis added.*

Contrary to the Examiner's position, I found no mention of including $CaCO_3$, $MgCO_3$ and $CaCO_3{\cdot}MgCO_3$ in Liu. It is immediately clear that teachings of including three salts of $CaCO_3$, $MgCO_3$ and $CaCO_3{\cdot}MgCO_3$ for stimulating bone-formation and bone-consolidation are not described, suggested or contemplated by Liu or by any references cited by the Examiner. Liu, at best, teaches including $CaCO_3$.

As an expert in the field, it is my expert opinion that it would not have been obvious to one of ordinary skill in the art to modify the compositions of Petersen et al as taught by Liu. As Liu teaches as "optionally the filler", those in the art understand that adding calcium carbonate is optional and thus not necessary to produce compositions for bone-formation and bone-consolidation. As such, those skilled in the art would **not** have predicted that including all three salts of $CaCO_3$, $MgCO_3$ and $CaCO_3{\cdot}MgCO_3$ in the bone-filling composition would provide superior results in stimulating bone-formation and bone-consolidation, which I have shown below.

It is also my expert opinion even if such compositions were made as proposed by the Examiner, the compositions, at best, would contain calcium carbonate. Such compositions are not the claimed compositions including 0.3-1 weight % $CaCO_3$, 0.3-1 weight % $MgCO_3$ and 0.5-1 weight % $CaCO_3{\cdot}MgCO_3$. The compositions proposed by the Examiner would fail to demonstrate the superior effect demonstrated by the applicant herein. No references alone or in combination provide the claimed compositions with superior property of stimulating bone-formation and bone-consolidation. I therefore assert that Petersen et al. and Liu taken singly or in combination do nothing to take away the inventiveness of our claimed bone-filling composition.

11. In order to demonstrate that the claimed compositions have an unexpectedly superior effect in bone formation and bone consolidation, a comparative test was undertaken.

I compared effect on bone-formation and bone-consolidation by measuring alkaline phosphatase, i.e. (ALP) assay, which is an art-known method for measuring bone-forming activity. In this test, the gel-type bone-filling compositions claimed in the present application were compared against several other types of compositions prepared according to the teachings of Petersen et al.

The comparison was conducted by seeding osteosarcoma cells on gels, each gel containing compositions described below, collecting the cells after seven days, and measuring ALP. The cell culture condition and ALP assay used in the test were set forth in Example A.

EXAMPLE A

Gels for Inventive Groups 1-3 and Control Groups 4-6 were prepared. Each of the gel compositions was prepared as follows:

[Table 1] Gel Compositions for Stimulating Bone-Formation and Bone-Consolidation

Composition		$CaSO_4 \cdot H_2O$	$CaCO_3$	$MgCO_3$	$CaCO_3 \cdot MgCO_3$	CMC:$CaSO_4 \cdot H_2O$
Inventive Group	No. 1	98.9g	0.3g	0.3g	0.3g	50:50
	No. 2	96.0g	0.5g	0.5g	1.0g	20:80
	No. 3	98.0g	0.4g	0.4g	1.2g	30:70
Control Group	No. 4	98.8g	-	-	-	50:50
	No. 5	98.0g	-	-	-	20:80
	No. 6	98.0g	-	-	-	30:70

CMC represents carboxymethylcellulose.

The inventive gel-type bone-filling compositions included (a) 20-80 weight % of a mixture containing calcium sulfate, $CaCO_3$, $MgCO_3$ and $CaCO_3 \cdot MgCO_3$ and (b) 80-20 weight % of a viscous biopolymer such as CMC. The counterpart control compositions included the same amounts of calcium sulfate and CMC without $CaCO_3$, $MgCO_3$ and $CaCO_3 \cdot MgCO_3$.

Human osteosarcoma cells, MG63, were obtained from Korean Cell Line Bank (KCLB). The cells were cultured in DMEM (Dulbecco's modified Eagle's medium) containing 10% (v/v) FBS (fetal bovine serum: from HyClone, USA) and 0.1% (w/v) gentamicin at the temperature of 37℃ and with 5% CO_2 under wet condition.

The cells were seeded on each gel and collected after culturing for 7 days. ALP assay was conducted three times for each group. The assay was conducted according to the protocol of ALP assay kit provided from Sigma, USA.

RESULTS

[Table 2] ALP Activity

Composition		ALP activity (nmol/min/μg)		
		Test 1	Test 2	Test 3
Inventive Group	No. 1	101	100	102
	No. 2	98	99	99
	No. 3	97	98	100
Control Group	No. 4	73	74	74
	No. 5	71	71	73
	No. 6	73	74	74

The ALP activities of the inventive compositions are 1.35 to 1.37 times higher than those of the control groups. The results clearly indicate that the claimed compositions including 0.3-1 weight % $CaCO_3$, 0.3-1 weight % $MgCO_3$ and 0.5-1 weight % $CaCO_3 \cdot MgCO_3$ have superior effect on bone-formation and bone-consolidation than the control compositions without such ingredients. Such results could not have been predicted by those of ordinary skill according to the teachings of Petersen et al. and Liu.

12. As confirmed by the comparative data, it has been found that the claimed compositions including 0.3-1 weight % $CaCO_3$, 0.3-1 weight % $MgCO_3$ and 0.5-1 weight % $CaCO_3 \cdot MgCO_3$ more effectively stimulate bone-formation and bone-consolidation. It is my exert opinion that artisans would not have been able to predict the composition including 0.3-1 weight % $CaCO_3$, 0.3-1 weight % $MgCO_3$ and 0.5-1 weight % $CaCO_3 \cdot MgCO_3$ would possess the unexpected property of stimulating bone-formation and bone-consolidation significantly effectively and such ingredients are so important for stimulating bone-formation and bone-consolidation.

As I have set forth above, it is clear that the combination of the references would still not render the invention claimed by applicants obvious.

13. I further declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful and false statements and like so made are punishable by fine or imprisonment, or both, under '1001 of Title 18 of the U.S. Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2007. 7. 24

Date

Cho, Byung Chae

Byung Chae Cho, M.D.

[Education]

· B.S. (1984) College of Medicine, Kyungpook National University (KNU).

· M.S. (1990) Plastic and Reconstructive Surgery, Graduate School of Medicine at KNU.

· Ph. D. (1992) Plastic and Reconstructive Surgery, Graduate School of Medicine at KNU.

[Professional Career]

· 1988. May-1992. Feb., Acquired Specialty in Plastic and Reconstructive Surgery in Kyungpook National University Hospital.

· 1994. Mar.-1996. Mar., Full-time Lecturer in College of Medicine at KNU.

· 1996. Apr.-2000. Mar., Adjunct Professor in College of Medicine at KNU.

· 1995. July, Visiting Professor of *Janggung* Hospital in Taipei, Taiwan.

· 1996. Sep.-1997. July, Visiting Professor of UIC in Chicago, USA.

· 1997. Aug., Visiting Professor of UCLA in LA, USA.

· 2000. Apr.- 2005. Mar., Adjunct Professor in College of Medicine at KNU.

· 2005. Apr.- 2007. May, Director in Dept. of Plastic and Reconstructive Surgery at Kyungpook National University Hospital.

· 2007. June.- Associate Professor in College of Medicine at KNU.

[Presently Occupying Status]

· 1998-present. Trustee of The Korean Burn Society, Director of The Korean Society for Microsurgery, Editing Committee of The Korean Society of Plastic and Reconstructive Surgeons.

[Awards and Honors]

· 2002. Science Awards, Association of Doctors in *Daegu*.

· 2003. The Outstanding Paper Awards, the 54th symposium of The Korean Society of Plastic and Reconstructive Surgeons.

· 2003, The Best Paper Awards, the 5th Symposium of Asia-Pacific Committee for Cleft lip and palate.

[Publications]

· Papers in Domestic Journal: 64.

· Papers in SCI: 49.

· Oral Presentation at International Symposium: 45.

· Books: 7.